

## Carcinogenicity of shift-work, painting, and fire-fighting

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In October, 2007, 24 scientists from ten countries met at the International Agency for Research on Cancer (IARC), Lyon, France, to assess the carcinogenicity of shift-work, painting, and fire-fighting. These assessments will be published as volume 98 of the IARC Monographs.<sup>1</sup>

About 15–20% of the working population in Europe and the USA is engaged in shift-work that involves nightwork, which is most prevalent (above 30%) in the health-care, industrial manufacturing, mining, transport, communication, leisure, and hospitality sectors. Among the many different patterns of shift-work, those including nightwork are the most disruptive for the circadian clock.

Six of eight epidemiological studies from various geographical regions, most notably two independent cohort studies of nurses engaged in shift-work at night,<sup>2,3</sup> have noted a modestly increased risk of breast cancer in long-term employees compared with those who are not engaged in shiftwork at night. These studies are limited by potential confounding and inconsistent definitions of shift-work, with several focused on a single profession. The incidence of breast cancer was also modestly increased in most cohorts of female flight attendants,<sup>4</sup> who also experience circadian disruption by frequently crossing time zones. Limitations of studies in these flight attendants include the potential for detection bias, proxy measures of exposure, and potential uncontrolled confounding by reproductive factors and cosmic radiation.

Several different rodent models have been used to test the effect of disruption of the circadian system

on tumour development. More than 20 studies investigated the effect of constant light, dim light at night, simulated chronic jet lag, or circadian timing of carcinogens, and most showed a major increase in tumour incidence. No clear effect was seen for light pulses at night or constant darkness. A similar number of studies investigated the effect of reduced nocturnal melatonin concentrations or removal of the pineal gland (where melatonin is produced) in tumour development and most showed increases in the incidence or growth of tumours.<sup>5,6</sup>

Exposure to light at night disturbs the circadian system with alterations of sleep-activity patterns, suppression of melatonin production, and deregulation of circadian genes involved in cancer-related pathways.<sup>7</sup> Inactivation of the circadian Period gene, *Per2*, promotes tumour development in mice,<sup>8</sup> and in human breast and endometrial tumours, the expression of PERIOD genes is inhibited.<sup>9</sup> In animals, melatonin suppression can lead to changes in the gonadotrophin axis.<sup>10</sup> In humans, sleep deprivation and the ensuing melatonin suppression lead to immunodeficiency.<sup>11,12</sup> For example, sleep deprivation suppresses natural killer-cell activity<sup>13</sup> and changes the T-helper 1/T-helper 2 cytokine balance, reducing cellular immune defence and surveillance.<sup>14</sup>

On the basis of "limited evidence in humans for the carcinogenicity of shift-work that involves nightwork", and "sufficient evidence in experimental animals for the carcinogenicity of light during the daily dark period (biological night)", the Working Group concluded that "shift-work that involves circadian

disruption is probably carcinogenic to humans" (Group 2A).<sup>15</sup>

Painters are potentially exposed to many chemicals used as pigments, extenders, binders, solvents, and additives. Painters can also be exposed to other workplace hazards, such as asbestos or crystalline silica.

Cohort and linkage studies of painters have shown consistent and significant increases in lung cancer compared with the general population. No information on tobacco smoking was available in the cohort studies; however, the increases are comparable to results from many case-control studies that controlled for smoking. A meta-analysis by the Working Group of all independent studies, including two recent large studies,<sup>16,17</sup> showed a significant excess risk of about 20% overall, and of 50% when the analysis was restricted to smoking-adjusted estimates from population-based case-control studies. Increased mortality from mesothelioma was consistently noted.<sup>18,19</sup>

Similarly, cohort and linkage studies showed consistent 20–25% increases in the occurrence of urinary bladder cancer in painters, and similar increases were noted in case-control studies that controlled for smoking.<sup>16,17,20</sup>

Although findings for lymphatic and haemopoietic cancers in painters were inconsistent, four of five case-control studies reported significant increases in childhood leukaemia associated with maternal exposure to paint. The risks tended to be greater when mothers were exposed before or during, rather than after, pregnancy,<sup>21,22</sup> and two studies showed some evidence of an increasing risk with increasing exposure.



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Overall, little information existed on specific work settings, and no particular agent could be identified from the available epidemiological studies as the cause of the increases in lung and urinary bladder cancers in painters.

Most cytogenetic studies on painters reported increased levels of genetic damage, such as chromosomal aberrations, micronucleus formation, sister chromatid exchange,<sup>23</sup> and DNA single-strand breaks. Several studies showed a dose-response association with duration of work. Stratified analyses by tobacco-smoking status generally showed similar results in smokers and non-smokers.

The Working Group concluded that there is "sufficient evidence in humans that occupational exposure as a painter causes cancers of the lung and urinary bladder". Additionally, there is "limited evidence in humans", mainly on the basis of studies of maternal exposure, that painting is associated with childhood leukaemia. Overall, occupational exposure as a painter is "carcinogenic to humans" (Group 1).<sup>15</sup>

Firefighters are exposed to many toxic combustion products, including many known, probable or possible carcinogens. These intermittent exposures can be intense, and short-term exposures can be high for respirable particulate matter and for some carcinogens, notably benzene, benzo[a]pyrene, 1,3-butadiene, and formaldehyde.

Although increases in various cancers in fire-fighters compared with the general population have been noted in several studies, consistent patterns are difficult to discern due to the large variations of exposures. The Working Group updated a recent meta-analysis of cancer in firefighters.<sup>24</sup> For three types of cancer the relative risks were consistently increased and the average increase was significant: testicular cancer (all six studies

showed increased risks, average relative risk 1.5), prostate cancer (increased risks in 18 of 21 studies, average relative risk 1.3), and non-Hodgkin lymphoma (increased risks in five of six studies, average relative risk 1.2).

For intermittent, but intense, exposures to highly variable complex mixtures, conventional measures, such as years of employment or number of firefighting runs, can be poor surrogates for exposure. The available epidemiological studies are inherently limited by this issue.

Acute and chronic inflammatory respiratory effects noted in firefighters<sup>25</sup> would provide a plausible mechanism for respiratory carcinogenesis. Studies that assess genotoxic effects in firefighters are few and inconclusive.

On the basis of "limited evidence of carcinogenicity in humans", the Working Group classified occupational exposure as a firefighter as "possibly carcinogenic to humans" (Group 2B).<sup>15</sup>

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#### Conflicts of interest

None

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#### Conflicts of interest

JA has received unrestricted research funding from Philips Lighting (Eindhoven, Netherlands), which was previously a joint patent holder for the use of short-wavelength light for adjusting circadian rhythms and maintaining alertness. JA is the Director of Stockgrand Ltd (Surrey, UK), which sells melatonin-measurement and 6-sulphatoxymelatonin-measurement technology. Finally, JA is a consultant at Alliance Pharmaceuticals UK, which develops melatonin products. JC undertakes consulting work for paint and pigment manufacturers, funded by European chemical industry trade associations and large industrial companies.

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